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Cancer of the Low and Middle Rectum: Local and Distant Recurrences, and Survival in 350 Radically Resected Patients

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The purpose of this study was to compare local recurrence, distant metastases, and survival rate in 350 patients with cancer of the middle and low rectum who underwent a radical abdominoperineal resection (APER) or a sphincter-saving resection (SSR) in our Institute.

There were 257 APER patients and 93 SSR patients, with a median follow-up of 77 months. At 5 years, the estimates in APER and SSR patients were respectively 11% and 30% for the incidence of pelvic recurrence, 18% and 8% for the incidence of distant metastases, and 64% and 73% for overall survival.

In the multivariate analysis it was found that Dukes' stage significantly affected pelvic recurrences, distant metastases rate and overall survival; histologic type affected only the pelvic recurrence rate. However, the final outcome of patients following APER or SSR was similar, suggesting that local failure per se does not affect long-term survival.

KEY WORDS: **rectal cancer, sphincter-saving surgery, abdominoperineal resection**

INTRODUCTION

Cancer of the colon and rectum represents a serious challenge for oncologic surgeons: it is the second most common site of cancer death in Italy, with more than 18,000 deaths per year. Its overall age-standardized rates have remained approximately constant in both sexes over the past 5 years [1].

Surgeons are directly involved in the therapeutic approach to rectal cancer not only because radical surgery plays a central role even in a multimodal strategy, including radiation therapy and chemotherapy, but also because the choice between radical surgery; that is, the Miles operation (abdominoperineal resection [APER]) and more conservative surgery (sphincter-saving resection [SSR]) might have some impact on the local recurrence rate, distant metastases, and survival.

The main purpose of this paper is to compare the oncologic outcome of patients who underwent radical or conservative surgery for cancer of the low and middle rectum at our institute.

MATERIALS AND METHODS

Out of 416 consecutive patients with cancer of the low and middle rectum who were surgically explored at the Istituto Nazionale Tumori of Milan between January 1970 and August 1988, we reviewed 350, who had undergone a radical operation and had been followed up at our institute. Demographic and clinical details are reported in Table I. All tumors were confined between 4 and 8 cm from the anal verge, as measured by sigmoidoscopy and rectal examination, and all were radically removed, meaning that there was an absence of gross cancer residue at the end of the operation and tumor-free margins of resection upon microscopical examination of the specimen.

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TABLE I. Demographic and Clinical Characteristics of Patients Surgically Treated for Cancer of the Middle and Lower Rectum*

	No. of patients (%)		
	APER (n = 257)	SSR (n = 93)	Overall (n = 350)
Distance from the anal verge (cm)			
4–5	142 (55)	11 (12)	153 (44)
6–8	115 (45)	82 (88)	197 (56)
Sex			
Male	157 (61)	48 (52)	205 (59)
Female	100 (39)	45 (48)	145 (41)
Age (yr)			
20–55	73 (28)	37 (40)	110 (31)
56–65	94 (37)	22 (24)	116 (33)
>65	90 (35)	34 (37)	124 (35)
Histological type			
Well-differentiated	64 (25)	20 (22)	84 (24)
Moderately differentiated	125 (49)	60 (65)	185 (53)
Poorly differentiated	7 (3)	2 (2)	9 (3)
Mucinous	25 (10)	7 (8)	32 (9)
Not specified	28 (11)	3 (3)	31 (9)
Other	7 (3)	1 (1)	8 (2)
Not reported	1 (0)	— (0)	1 (0)
Lymph nodes			
N−	168 (65)	57 (61)	225 (64)
N+	80 (31)	34 (37)	116 (33)
Unknown	9 (4)	2 (2)	11 (3)
Dukes' stage			
A	61 (24)	25 (27)	86 (25)
B	95 (37)	32 (34)	127 (36)
C	80 (31)	34 (37)	114 (33)
Unknown	21 (8)	2 (2)	23 (7)
Postoperative therapy			
No	191 (74)	68 (73)	259 (74)
Yes	66 (26)	25 (27)	91 (26)
Period of surgery (yr)			
1970–1974	68 (26)	4 (4)	72 (21)
1975–1979	95 (37)	10 (11)	105 (30)
1980–1984	68 (26)	50 (54)	118 (34)
1985–1988	26 (10)	29 (31)	55 (16)

*APER, abdominoperineal resection; SSR, sphincter-saving resection.

In 257 patients, the surgical procedure was an APER, usually with ligation of the vascular pedicle distal to the left colic or the colosigmoid artery, but with clearance of the fatty tissue around the inferior mesenteric artery if lymph nodes became apparent during the operation. A low or very low anterior resection (sphincter-saving resection, or SSR) was performed in 93 patients with the same extension on the vascular pedicle as for the APER. We made no deliberate attempt to clear the mesorectum, but a total rectal excision including the mesorectum was performed at least in the lesions of the lower rectum in order to achieve a safe distal margin of transection, which averaged 2 cm of unstretched tissue, plus the circular specimen remaining in the cartridge in stapled anastomoses. In these cases, we performed a colorectal or coloanal canal abdominal anastomosis following a previously described standard technique [2].

The final choice between APER and SSR was left to the judgment of the operating surgeon; however, there was a general policy of performing an SSR whenever the ratio tumor volume/pelvic volume permitted safe removal of the rectal cancer, and at least 1 cm of healthy distal margin was available for the anastomosis. Mortality for the two operations was 4.3% and 3.2%, respectively, (P = NS) and was not computed in the analysis of local recurrence, distant metastases, and survival.

Follow-up was usually planned on a basis of 4-month intervals for 5 years, and subsequently twice a year. It included a clinical examination, a liver function test, research for blood in the stools, a carcinoembryonic assay (CEA), endoscopy, or barium enema, and liver scanning. Chest radiographs were taken twice a year for the first 3 years. In the second half of our study period, more sophisticated imaging techniques were employed, such as abdominal sonography on a routine basis, and computed tomography (CT) scan or magnetic resonance imaging (MRI) when required. Bone scanning and scintigraphy with anti-CEA antibodies were employed more rarely.

When a cancer relapse was suspected at the clinical examination or during the routine follow-up, a diagnostic workup was planned to better define its presence and extent. Histological confirmation was the rule under the guide of CT or ultrasound (US), but bone lesions or some lesions deep in the pelvis were accepted as neoplastic deposit when associated with a significant symptomatology and/or progression over time and/or elevations of CEA. Depending on the site of the relapses, these were defined as local, i.e., pelvic, and distant, i.e., extrapelvic. The median follow-up of the patients was 77 months.

As regards the pathologic examination, surgical specimens were taken from the operating theater and examined without previous fixation. Two or three samples were taken from the most infiltrating part of the tumor, and lymph nodes were searched by hand dissection. Samples were also taken from the distal and proximal margins of the resection in all cases. The tumors were classified into well, moderately, and poorly differentiated, and the original Dukes' stage (A, B, and C) was used for pathologic staging.

STATISTICAL METHODS

The outcomes considered were pelvic recurrences, distant metastases, second primaries, and deaths from any cause whatsoever. Survival time was defined as the interval from surgery to the occurrence of death, or to the last follow-up assessment available for living patients.

Time to pelvic recurrence, distant metastases, or second primary was calculated as the time elapsed from surgery to the occurrence of the first neoplastic event, or to the last follow-up assessment available or death without any

evidence of disease (NED) if no neoplastic event occurred. Overall survival curves were obtained using the Kaplan–Meier method [3]. Crude cumulative incidence curves were obtained as described by Kalbfleish and Prentice, regarding the different outcomes as competing events [4].

We investigated the following prognostic factors, categorized as shown in the tables: sex, age, histologic type, Dukes' stage, surgery, calendar period of surgery, and postoperative adjuvant therapy. Univariate analyses were performed by means of the log-rank test [5]. Those factors achieving a P-value of ≤ 0.20 were entered into a Cox multiple regression model and then selected by means of a backward procedure. Indicator variables were used to specify the categories of each factor. Surgery was always retained in the model independent of its significance.

For pelvic recurrences and distant metastases, the analysis was carried out by considering all failures other than the one being studied as censored observations, thus relying on cause-specific hazards [4].

RESULTS

The main characteristics of the 350 patients analyzed are reported in Table I. The distribution of these characteristics was comparable in the two treatment groups, except for calendar period of surgery, as SSR has been adopted more frequently in recent years.

The events observed during the follow-up were the following (in number of patients): pelvic recurrence, 54; distant metastases, 50; synchronous pelvic recurrence and distant metastases, 13; and second primary, 14.

One-hundred thirty-five deaths occurred, 14 of which were postoperative and 23 in NED patients. Synchronous events were analyzed both as pelvic recurrences and distant metastases in univariate and multivariate analyses.

Figures 1–3 report the curves of overall survival and cumulative incidence of pelvic recurrences, distant metastases, and other events (second primaries and NED deaths), depending on which treatment was given.

It is noteworthy that the vast majority of pelvic recurrences were confined to the first two to three postoperative years following APER, while it appeared more delayed and less frequent following SSR.

At five years, the estimated incidences for SSR and APER patients were respectively 30% and 11% for pelvic recurrences, 8% and 18% for distant metastases, and 73% and 64% for overall survival.

By univariate analyses, Dukes' stage and histologic type achieved statistical significance for pelvic recurrences, distant metastases, and survival.

Postoperative adjuvant therapy was statistically significant for distant metastases and survival. The prognosis was less favorable for treated patients, however, as compared with nontreated ones, because patients at high risk for relapse were selected for adjuvant therapy. Finally,

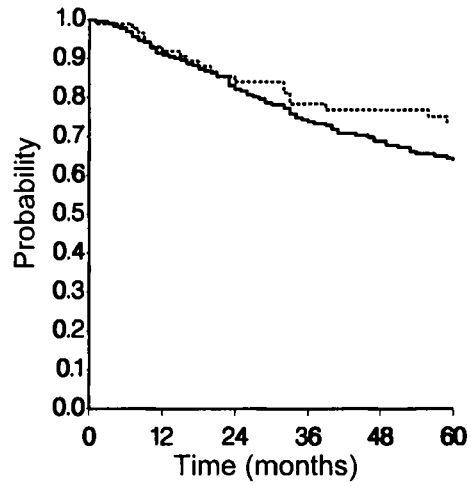

Fig. 1. Overall survival in patients undergoing abdominoperineal resection (——) or sphincter-saving resection (– – –).

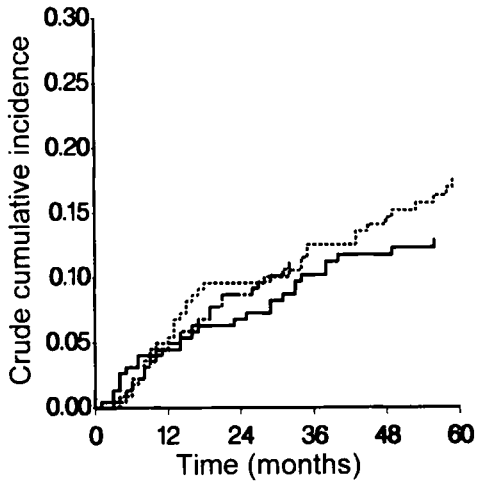

Fig. 2. Crude cumulative incidence of pelvic recurrences (· – ·), distant metastases (– – –), and other events (——) in patients undergoing abdominoperineal resection.

the type of surgery significantly affected the onset of pelvic recurrence, since the rate of their occurrence was higher after SSR.

Multivariate analyses were performed on 314 patients, after excluding postoperative deaths and subjects with incomplete information on prognostic variables. The results are reported in Tables II–IV, and confirm the impact of the surgical procedure and Dukes' stage on pelvic recurrences, of Dukes' stage on distant metastases, and of Dukes' stage and histology on the overall survival rate.

DISCUSSION

Surgeons involved in caring for patients with cancer of the middle and distal rectum are usually faced with

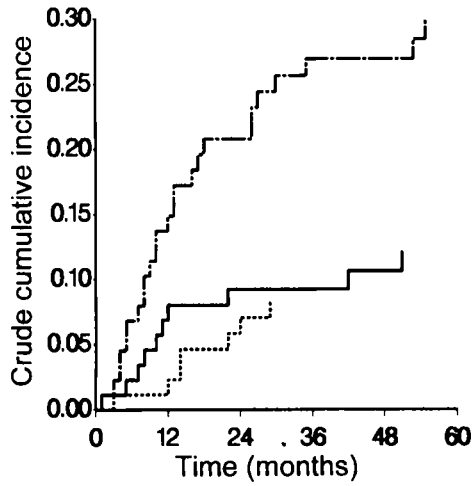

Fig. 3. Crude cumultive incidence of pelvic recurrences (· – ·), distant metastases (– – –), and other events (——) in patients undergoing sphincter-saving resection.

TABLE II. Results With the Cox Model on Pelvic Recurrences*

	HR	95% CI	χ^2	df	*P*
Surgery			14.05	1	<0.0001
SSR vs. APER	2.64	(1.61–4.32)			
Dukes' stage			40.81	2	0.0002
B vs. A	2.69	(1.06–6.78)			
C vs. A	8.85	(3.73–21.00)			
C vs. B	3.29	(1.88–5.77)			

APER, abdominoperineal resection; SSR, sphincter-saving resection. *Hazard ratio (HR) estimate and corresponding 95% confidence interval (CI); likelihood ratio test chi-square (χ^2), and corresponding degrees of freedom (df) and *P*-value.

TABLE III. Results With the Cox Model on Distant Metastases*

	HR	95% CI	χ^2	df	*P*
Surgery			0.17	1	0.6781
SSR vs. APER	0.88	(0.47–1.63)			
Dukes' stage			31.98	2	<0.0001
B vs. A	2.76	(1.11–6.88)			
C vs. A	7.86	(3.27–18.90)			
C vs. B	2.85	(1.63–5.00)			

APER, abdominoperineal resection; SSR, sphincter-saving resection. *Hazard ratio (HR) estimate and corresponding 95% confidence interval (CI); likelihood ratio test chi-square (χ^2), and corresponding degrees of freedom (df) and *P*-value.

two problems: first, to achieve the best possible oncologic result, and second, to spare the sphincter function.

The aim of this retrospective investigation on a large series of cancers of the middle and low rectum uniformly treated by a surgical staff at the Istituto Nazionale Tumori of Milan was to investigate the prognostic impact of radical and conservative surgery adjusting for other prognostic factors.

Although our conclusions should be accepted with caution, since they do not result from a randomized clinical trial, nevertheless our data show that Dukes' stage has major prognostic relevance in determining the local recurrence rate, the appearance of distant metastases, and the survival rate.

We also observed a statistically significant prognostic effect of tumor histology on survival. After adjusting for these factors in the multivariate analysis the type of surgery was shown to affect pelvic recurrence, in that it occurred more frequently after SSR.

Two major questions arising from this study are whether the higher pelvic recurrence rate of SSR versus APER is in keeping with the current literature and whether our pelvic recurrence rate after SSR is excessively high. Despite the fact that the literature dealing with cancer of the rectum is extensive, there are relatively few papers reporting a statistical comparison between APER and SSR in homogeneous series of patients with cancer of the middle and low rectum [6–15] (Table V). Nevertheless, 4 analyses out of 12 [7,11,15] collected from the literature and encompassing an overall number of 1,400 patients reported a statistically higher rate of pelvic recurrences after SSR than after APER. In addition, no study has ever demonstrated an advantage for local recurrence with SSR. Therefore, our pelvic recurrence rates are very much in agreement with data from the literature, which reported a median recurrence rate of 19% (range: 5–50) and 22% (range: 10–83) after APER and SSR, respectively, in a cumulative number of more than 2,900 patients (Table V).

These data support the contention that for these tumors APER is presently the "gold standard" operation [16], offering the widest possible local resection and that SSR, at the very best, can only parallel the results of APER but not improve upon them. The volume of SSR resection is in fact the same as that of APER as regards the proximal margin, which usually falls at the origin of the left colic or the colosigmoid artery and at the passage between descending and sigmoid colon. On the lateral pelvic sides the surgeon embarking on an SSR may be more conservative in order to maintain an optimal blood supply to the rectal stump to be anastomosed, whereas distally the resection is obviously less radical. A possible explanation for the higher incidence of local recurrences and for their delayed onset in patients undergoing SSR, as compared to APER, is that some of these relapses involving the bowel in the pelvis are due to a metachronous cancer at the anastomosis. Metachronous cancers occur in up to 5% of patients during follow-up [17–19], and especially those occurring more than 2 years after surgery may in fact represent a new carcinogenesis at the anastomosis [20,21], due to the presence at this level of a zone of increased crypt cell production [21,22]. Although some

TABLE IV. Results With the Cox Model on Overall Survival*

	HR	95% CI	χ^2	df	*P*
Surgery			1.98	1	0.1595
SSR vs. APER	0.72	(0.46–1.15)			
Histology			10.83	4	0.0286
Not specified and other vs. well-differentiated	1.55	(0.76–3.17)			
Moderate vs. well-differentiated	1.39	(0.81–2.39)			
Mucinous vs. well-differentiated	1.35	(0.65–2.79)			
Poor vs. well-differentiated	5.59	(2.24–13.95)			
Dukes' stage			31.50	2	<0.0001
B vs. A	1.57	(0.87–2.83)			
C vs. A	4.07	(2.30–7.20)			
C vs. B	2.59	(1.68–4.01)			

APER, abdominoperineal resection; SSR, sphincter-saving resection.
*Hazard ratio (HR) estimate and corresponding 95% confidence interval (CI); likelihood ratio test chi-square (χ^2), and corresponding degrees of freedom (df) and *P*-value.

TABLE V. Pelvic Recurrence Rate After Abdominoperineal Resection Versus Sphincter-Saving Resection in Cancer of the Middle and Low Rectum

	APER		SSR		
Investigators	No. of patients	Rate	No. of patients	Rate	*P*
Pilipsen et al. [7][a]	28	21.4	175	31.4	NS
Pilipsen et al. [7][b]	478	12	370	18	0.011
McDermott et al. [8][c]	333	23	355	22	NS
Williams et al. [9][d]	74	19	74	14	NS
Kennedy et al. [10][e]	20	50	70	36	NS
Neville et al. [11][c]	47	13	38	32	0.035
Secco et al. [12]	30	26	9	67	NS
Tagliacozzo and Accordino [13][f]	38	21	70	22	NS
Jatzko et al. [14][g]	69	14	36	10	NS
Wolmark and Fisher [15][h]	232	5	181	13	0.004

APER, abdominoperineal resection; SSR, sphincter-saving resection; NS, not significant at 5% level.
[a]Midrectum (6–11 cm).
[b]Below peritoneal reflection.
[c]Midrectum.
[d]Well matched, follow-up 2 years.
[e]Balanced by stage.
[f]Dukes' B and C.
[g]Balanced by stage and grading.
[h]Dukes' B and C.

surgeons will surely disagree with this statement, it is our opinion that discrepancies among different surgical series probably reflect different criteria of pathological staging, which also affect the surgeon's final judgment as to the extent of surgery. For this reason comparisons between APER and SSR should be made within series from the same institution, and not among different series from different institutions.

In fact it is noteworthy that Rubio et al. [23] clearly demonstrated in 1977 that Dukes' staging is dependent on the number of sections from the tumor sample. In the recent experience of our Pathology Department, careful examination of the mesorectum has shown extramural neoplastic embolism in approximately 50% of Dukes' A cases, which would have been missed with a more superficial examination.

We acknowledge the value of the mesorectal excision in the treatment of cancer of the extraperitoneal rectum, as pointed out by our English colleagues in their excellent study [24–27]. Nevertheless we believe that a recurrrence rate after SSR and APER of 6.4% and 14%, respectively, in the experience of the team which pioneered the total

excision of the mesorectum [28] does not support the conclusion that there is an advantage of radicality of SSR, but simply indicates a selection of favorable cases submitted to SSR, such as proximal location [28] or well-differentiated tumors [14].

As regards the survival rate, our figures are in perfect agreement with the extensive literature [8,9,15,29–35] showing that irrespective of the absolute values, there is no difference in the 5-year survival after APER or SSR in cancer of the extraperitoneal rectum. Moreover, our data paralleled the results of the NSABP prospective trial [15], which reported that in a total number of 413 patients no difference was found in the 4-year survival in APER versus SSR, despite a statistically higher prevalence of pelvic recurrences in the SSR group. These data are also in keeping with the result of studies on radiation given before or after operations, which is able to decrease the local recurrence rate significantly without affecting survival [36–38].

In conclusion, the final results of this study show that the two operations are quite similar for the long-term prognosis even if SSR have a higher pelvic recurrence rate. This study, as well as data from the literature, does not identify which group of patients could possibly benefit from an SSR without having a higher risk of pelvic recurrences. However, since the main difference between SSR versus APER lies in the lesser distal clearance achieved with SSR, we suggest that patients with distal tumors that are bulky, have a safe transection margin of less than 1 cm and are not amenable to an adjuvant therapy should be candidates for APER. In this regard, it is noteworthy that a recent randomized clinical trial on postoperative radiation and chemotherapy [39] showed a reduction in death rate that was minimal in patients with APER and striking in those with anterior resection. These data, if confirmed in subsequent studies, warrant further consideration in the choice between the two surgical procedures.

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